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EXAMINER	
NIEBAUER, RONALD T	
ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/565,903	GIANNI ET AL.	
	Examiner	Art Unit	
	RONALD T. NIEBAUER	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-30,32-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-30,32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/13/09 has been entered.

Applicants arguments and affidavit filed 11/13/09 and supplemental response filed 11/16/09 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Claims 1-26,31 have been cancelled.

Claims 27-30,32-36 are under consideration.

Claim Rejections - 35 USC § 103

The 103 rejections are identical to the rejections set forth in the previous office action.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-30,32,34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al (In vivo v16 2002 pages 535-540 as cited previously) and Merck Manual (entry for neutropenia, as cited previously) and Hattori et al (Nature Medicine v8 2002 pages 841-849 as cited previously).

Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells for use in transplantation in particular autologous or allogenic transplantation and to treat neutropenia for example. Robinson does not define neutropenia. The Merck Manual (accessed from http://www.merck.com/mmhe entry for neutropenia) teaches that neutropenia is an abnormally low number of neutrophils in the blood (first sentence). The Merck Manual teach that neutrophils are white blood cells (page 1 9th sentence). Thus, Robinson motivates treating those with a low number of neutrophils in the blood as in claim 30. The Merck Manual is cited to show a universal fact and definition and as such the date of the reference is not relevant (see MPEP section 2124). Further, since Robinson specifically teach the use for autologous or allogenic transplantation, Robinson motivate the patient population as recited in claim 30 and dependent claims. Robinson recognize that rapid clearance is a disadvantage of recombinant molecules and that a goal is to achieve clinical efficacy with fewer injections (abstract). Robinson teach (page 535 2nd column see also titles of

reference 2) that G-CSF has been used in the clinic following chemotherapy thus meeting the patient population recited in claim 30 of the instant invention. Robinson teach (page 535 2nd column see also titles of references 5-7 on page 538) that G-CSF was administered to improve neutrophil recovery and significantly reduced the period of neutropenia.

Robinson does not expressly teach the use of G-CSF together with the use of placental growth factor.

Robinson recognize that rapid clearance is a disadvantage of recombinant molecules and that a goal is to achieve clinical efficacy with fewer injections (abstract). Robinson recognize optimization of administration (page 537 'summary' section). Thus one would be motivated to look for alternate strategies and techniques to achieve such a goal.

Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4). Hattori teach that the studies suggest that PlGF which is endowed with a low toxicity profile provides a strategy to induce hematopoiesis after chemotherapy/radiation (compare claim 30 of the instant invention), or in hematological disorders (page 842 first paragraph).

Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells. The work of Hattori (page 844 last paragraph to page 845 first paragraph and figure 4) suggest that placental growth factor mobilize hematopoietic stem cells. As such, the prior art included both elements of the instantly claimed compositions: G-CSF and PlGF. One of skill in the art could have combined the elements as

claimed by known methods with no change in their respective function (mobilize hematopoietic stem cells) and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Since Hattori teach that PlGF augmented the number of pluripotent hematopoietic cells by 20-fold (page 845 first column and Figure 4) and Robinson teach that G-CSF is widely used (abstract) one would have a reasonable expectation of success.

Further, section 2144.06 of the MPEP states that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition. The idea of combining them logically flows from their having been individually taught in the prior art. Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells. The work of Hattori (page 844 last paragraph to page 845 first paragraph and figure 4) suggest that placental growth factor mobilize hematopoietic stem cells. Therefore, the combination of G-CSF and PlGF to mobilize hematopoietic stem cells logically flows from their having been individually taught in the prior art.

Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) as recited in claim 27. Although Hattori does not expressly teach the use of the recombinant human PlGF it would have been obvious to use a recombinant and human version of the molecule since such substitutions are well-known in the art. The substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. As such, the limitations of claim 28 are met.

Since Robinson teach that the G-CSF can be administered by infusion or injection (abstract, page 535 2nd column) one would be motivated to formulate the G-CSF and PlGF

combination in such forms, for ease of administration for example, thus meeting the limitations recited in claim 29. It is noted that claim 27 for example, allows the inclusion of excipients. Further, it would have been obvious to administer the G-CSF and PlGF either separately in sequence or simultaneously since those are the typical well-known modes of administering combinations thus meeting the limitations recited in claims 32,34-36 of the instant invention. Further, since Robinson (page 535 2nd column) recognize the use of daily injections one would be motivated to use daily administrations as recited in claim 36.

It is noted that claim 27 states 'wherein said composition is able to….'. Since the combination of Robinson and Hattori teach the combination recited in the instant claims the properties recited in the claims are necessarily present absence evidence to the contrary (see MPEP section 2112.01).

It is noted that claim 35 recites 'consisting essentially of'. Section 2111.03 of the MPEP states:

> The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention.
> For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising."

In the instant case, there is no clear indication in the specification or claims as to what the basic and novel characteristics are. Therefore, "consisting essentially of" will be construed as equivalent to "comprising" in claim 35.

Claims 27-30,32-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al (In vivo v16 2002 pages 535-540 as cited previously) and Merck Manual (entry

for neutropenia, as cited previously) and Hattori et al (Nature Medicine v8 2002 pages 841-849 as cited previously) and Anderlini et al (Journal of the American Society of Hematology v90 1997 page 903-908 as cited previoulsy) and Carmeliet (US 7,105,168 as cited previously).

As discussed above, Robinson, Merck Manual, and Hattori render obvious claims 27-30,32,34-36.

It would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g.doses), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* MPEP § 2145.05).

Anderlini teach that doses of, for example, 24 ug/kg/day (page 904 first column 16th line from the bottom) of recombinant human G-CSF have been used previously thus meeting the range as recited in claim 33 of the instant invention. Carmeliet teach PlGF (specifically human PlGF column 6 line 9) use as part of treatments such as for transplantations (column 3 line 22) and specifically teach that recombinant PlGF is used (column 15 line 7) and PlGF dosages 'of 15ug/kg/day of active ingredient up to 100 ug/kg/day or higher' (column 15 line 12) are deemed to be a safe level thus meeting the range as recited in claim 33 of the instant invention. Although the references do not necessarily teach G-CSF and PlGF for the identical use as in the instant invention, one of skill in the art would use the prior art doses as starting points for the routine optimization.

Response to Arguments 103 rejection

Applicants argue (reply pages 2-3) that the references teach away since Robinson teaches fluctuations and Hattori teaches intravenous administration.

Applicants argue (reply pages 3-4) that Hattori leads to an inoperative composition and refers to the declaration and specification and argue that PlGF is ineffective when administered alone.

Applicants argue (reply page 4) that an adenoviral system is a facilitated system. The declaration (page 2) argues that adenoviral expression of growth factor cannot at all be predictive.

The declaration argues (page 4) that injection of adenoviral vector may induce cytokines.

Applicants argue (reply page 4-5) that the evidence shows that PlGF alone is ineffective.

Applicants argue (reply page 5-7) that one would not equate administration of AdPlGF to administration of PlGF. Applicants argue that one must consider the technical knowledge in the field.

Applicants argue (reply page 7) that consisting essentially of excludes certain administrations.

Applicants argue (reply pages 7-8) that one would have no reasonable expectation of success.

Applicants argue (reply page 8) that there are unexpected results and that the proper comparison is between rmPlGF alone and rmPlGF in combination with GCSF.

Applicants argue (reply page 8) that one would expect that the combination has only the effect of GCSF alone not greater than the effect with GCSF alone.

Applicants argue (reply pages 9-11) that Applicants data shows that one would not have an expectation of success.

Applicants argue (reply page 11) that the evidence in the specification is valid.

Applicants argue (reply page 12) that differences are based on the intrinsic nature of the substances.

Applicants argue (reply pages 12-15) that one cannot rely on Hattori and the correct comparison is to PlGF administered alone.

Applicants argue (reply pages 14-15, declaration pages 4-7) that the results are unexpected.

Applicant's arguments and affidavit filed 11/13/09 and supplemental response filed 11/16/09 have been fully considered but they are not persuasive.

Although Applicants argue (reply pages 2-3) that the references teach away since Robinson teaches fluctuations and Hattori teaches intravenous administration, the exact quote ('the direct administration of recombinant GCSF…') that applicants refer to can not be located. Robinson acknowledges fluctuations (page 537 2nd column first paragraph of 'summary') and states that biological efficacy can be achieved if the protein is administered once or twice daily. Thus Robinson does not teach away since Robinson expressly teach that biological efficacy can be achieved. Robinson expressly states that the protein can be administered 'to achieve biological efficacy' (page 537 section 'summary'). Since biological efficacy can be achieved one would recognize that G-CSF administration is desirable and can be used with a reasonable expectation of success. Further, it is noted that claim 27 for example does not require an administration.

Although applicants argue that Hattori teach intravenous administration it is noted that certain claims do not specify a mode of administration or mention a parenteral route (see claim 32). Intravenous administration is a parenteral route thus there is not a teaching away.

Although Applicants argue (reply pages 3-4) that Hattori leads to an inoperative composition and refers to the declaration and specification and argue that PlGF is ineffective when administered alone, section 2121 of the MPEP states that prior art is presumed enabled. Thus there is a reasonable basis that the composition of Hattori is operative. In fact, Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4). Hattori teach that the studies suggest that PlGF which is endowed with a low toxicity profile provides a strategy to induce hematopoiesis after chemotherapy/radiation, or in hematological disorders (page 842 first paragraph). Further, MPEP 2143.02 III states that predictability is determined at the time of the invention. As explained in the rejection one would have a reasonable expectation of success based on the express teachings of the references. Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells for use in transplantation in particular autologous or allogenic transplantation and to treat neutropenia for example. Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4). Hattori teach that the studies suggest that PlGF which is endowed with a low toxicity profile provides a strategy to induce hematopoiesis after

chemotherapy/radiation (compare claim 30 of the instant invention), or in hematological disorders (page 842 first paragraph). Since Hattori teach that PlGF augmented the number of pluripotent hematopoietic cells by 20-fold (page 845 first column and Figure 4) and Robinson teach that G-CSF is widely used (abstract) one would have a reasonable expectation of success. There is nothing of record to show that the data of the applicant is prior art. At the time of the invention one would not have been aware of applicants data. Thus, at the time of the invention (see MPEP 2143.02 III) one would have a reasonable expectation of success based on the teachings of Hattori and Robinson. Further, MPEP section 2121.01 II states that even if a reference is inoperative it is prior art for all that it teaches. Thus Hattori is proper prior art. Further, it is noted that the instant claims are to compositions or methods that require at least two active agents, not just PlGF.

Although Applicants argue (reply page 4) that an adenoviral system is a facilitated system and the declaration (page 2) argues that adenoviral expression of growth factor cannot at all be predictive, it is noted that the instant rejection is a 103 rejection. As such, any single reference does not necessarily anticipate the claims. MPEP 2143.02 II states that obviousness does not require absolute predictability. Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4). Thus one would expect that placental growth factor causes such effects. Since Hattori teach that the studies suggest that PlGF which is endowed with a low toxicity profile provides a strategy to induce hematopoiesis after chemotherapy/radiation or in hematological disorders (page 842 first paragraph) one would be

motivated to go from the model system of Hattori to actual administrations to humans for example. Although applicants argue that the model system cannot be predictive, if such assertion were true then no model systems would be used. One would be motivated to use administrations as in Robinson. Since Hattori teach that PlGF augmented the number of pluripotent hematopoietic cells by 20-fold (page 845 first column and Figure 4) and Robinson teach that G-CSF is widely used (abstract) one would have a reasonable expectation of success.

Although the declaration argues (page 4) that injection of adenoviral vector may induce cytokines, the instant claims do not recite cytokines. Further, there is no evidence to support such opinion.

Although Applicants argue (reply page 4-5) that the evidence shows that PlGF alone is ineffective, MPEP 2143.02 III states that predictability is determined at the time of the invention. As explained in the rejection one would have a reasonable expectation of success based on the express teachings of the references. Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4). Hattori teach that the studies suggest that PlGF which is endowed with a low toxicity profile provides a strategy to induce hematopoiesis after chemotherapy/radiation), or in hematological disorders (page 842 first paragraph). Since Hattori teach that PlGF augmented the number of pluripotent hematopoietic cells by 20-fold (page 845 first column and Figure 4) one would have a reasonable expectation of success. There is nothing of record to show that the data of the applicant is prior art. At the time of the invention one would not have been aware of applicants data. Thus, at the time of the invention (see MPEP

2143.02 III) one would have a reasonable expectation of success based on the teachings of Hattori and Robinson. Section 2143.01 II of the MPEP discusses situations in which the prior art conflicts. In the instant case, the record shows that the prior art (i.e. Hattori) would lead one to use PlGF. There is no prior art of record to conflict Hattori. Further, the instant claims require either compositions or methods that have 2 active agents. Thus the claims are not to administration of PlGF alone.

Although Applicants argue (reply page 5-7) that one would not equate administration of AdPlGF to administration of PlGF and that one must consider the technical knowledge in the field, the instant rejection is a 103 rejection not a 102 rejection. Hattori identify PlGF as an active agent. Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4). Hattori teach that the studies suggest that PlGF which is endowed with a low toxicity profile provides a strategy to induce hematopoiesis after chemotherapy/radiation), or in hematological disorders (page 842 first paragraph). Thus the technical knowledge in the art points towards use of PlGF. Although there are differences in administration in model systems compared to other systems there is no basis to expect that other systems would destroy the activity of PlGF. In fact, Hattori teach that the studies suggest that PlGF which is endowed with a low toxicity profile provides a strategy to induce hematopoiesis after chemotherapy/radiation), or in hematological disorders (page 842 first paragraph). Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells. The work of Hattori (page 844 last paragraph to page 845 first paragraph and figure

4) suggest that placental growth factor mobilize hematopoietic stem cells. Therefore, the combination of G-CSF and PlGF to mobilize hematopoietic stem cells logically flows from their having been individually taught in the prior art.

Although Applicants argue (reply page 7) that consisting essentially of excludes certain administrations, Section 2111.03 of the MPEP states:

> The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention.
> For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising."

In the instant case, there is no clear indication in the specification or claims as to what the basic and novel characteristics are. Therefore, "consisting essentially of" will be construed as equivalent to "comprising" in claim 35. In the instant case, the model system of Hattori shows the benefits of PlGF. In fact, Hattori suggests that PlGF which is endowed with a low toxicity profile provides a strategy to induce hematopoiesis after chemotherapy/radiation), or in hematological disorders (page 842 first paragraph).

Although Applicants argue (reply pages 7-8) that one would have no reasonable expectation of success, Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells for use in transplantation in particular autologous or allogenic transplantation and to treat neutropenia for example. Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4). Hattori teach that the studies suggest that PlGF which is endowed with a low toxicity profile provides a strategy to induce hematopoiesis after chemotherapy/radiation (compare claim 30 of the instant

invention), or in hematological disorders (page 842 first paragraph). Since Hattori teach that PlGF augmented the number of pluripotent hematopoietic cells by 20-fold (page 845 first column and Figure 4) and Robinson teach that G-CSF is widely used (abstract) one would have a reasonable expectation of success. Further, section 2144.06 of the MPEP states that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition. The idea of combining them logically flows from their having been individually taught in the prior art. Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells. The work of Hattori (page 844 last paragraph to page 845 first paragraph and figure 4) suggest that placental growth factor mobilize hematopoietic stem cells. Therefore, the combination of G-CSF and PlGF to mobilize hematopoietic stem cells logically flows from their having been individually taught in the prior art. It is noted that section 2141 of the MPEP states:

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton."KSR, 550 U.S. at ___, 82 USPQ2d at 1397. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle."Id. Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ."Id. at ___, 82 USPQ2d at 1396.

In the instant case, although Hattori teach the use of an adenovirus one of skill in the art would not be limited to use of an adenovirus as a method of delivering a protein. Since Robinson teach that G-CSF can be administered by infusion or injection (abstract, page 535 2nd column) one would be motivated to formulate the G-CSF and PlGF combination in such forms, for ease of

administration for example. In other words, one would be motivated to standardize the mode of administration so that the G-CSF and PlGF could be co-administered. One of skill in the art would recognize that the active protein ingredient that is expressed via the adenovirus (i.e. PlGF) is an active protein ingredient like that which is delivered directly via injection of a protein for example (i.e. PlGF).

Although Applicants argue (reply page 8) that there are unexpected results and that the proper comparison is between rmPlGF alone and rmPlGF in combination with GCSF, MPEP section 716.02(c) II states that expected beneficial results are evidence of obviousness. The instant claims are drawn to compositions or methods using 2 active agents. However, the prior art already recognizes using the agents individually for certain applications. Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells. The work of Hattori (page 844 last paragraph to page 845 first paragraph and figure 4) suggest that placental growth factor mobilize hematopoietic stem cells. Therefore, the combination of G-CSF and PlGF to mobilize hematopoietic stem cells logically flows from their having been individually taught in the prior art. Since Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4) and teach that the studies suggest that PlGF which is endowed with a low toxicity profile provides a strategy to induce hematopoiesis after chemotherapy/radiation (compare claim 30 of the instant invention), or in hematological disorders (page 842 first paragraph) one would expect PlGF to mobilize cells, for example. However, the instant claims are not to the sole administration of

PlGF. Thus studies involving PlGF alone are not commensurate in scope with the claims (see MPEP 716.02(d)). In the instant case, Robinson teach that G-CSF is widely used to mobilize stem cells, for example (abstract). Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4) and that PlGF provides a novel strategy for use after chemotherapy (page 842 first column). Thus, the prior art teach positive results for each of the components. Further, Hattori teach that PlGF augmented the number of pluripotent hematopoietic cells by 20-fold (page 845 first column and Figure 4). As such, one would expect an increase when using PlGF. Since Hattori teach 20-fold increases, the 1.5fold increases are not deemed unexpected, even if one accepted that increases might vary based on the mode of administration. In the instant case, the teachings of the prior art lead to a general expectation of increases when PlGF is used.

Although Applicants argue (reply page 8) that one would expect that the combination has only the effect of GCSF alone not greater than the effect with GCSF alone, such expectation is inconsistent with Hattori. Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4). Hattori teach that the studies suggest that PlGF which is endowed with a low toxicity profile provides a strategy to induce hematopoiesis after chemotherapy/radiation (compare claim 30 of the instant invention), or in hematological disorders (page 842 first

paragraph). Thus Hattori recognizes the beneficial effects of PlGF. MPEP section 716.02(c) II states that expected beneficial results are evidence of obviousness:

> "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." In re Gershon, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967) (resultant decrease of dental enamel solubility accomplished by adding an acidic buffering agent to a fluoride containing dentifrice was expected based on the teaching of the prior art); Ex parte Blanc, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989) (Claims at issue were directed to a process of sterilizing a polyolefinic composition which contains an antioxidant with high-energy radiation. Although evidence was presented in appellant's specification showing that particular antioxidants are effective, the Board concluded that these beneficial results would have been expected because one of the references taught a claimed antioxidant is very efficient and provides better results compared with other prior art antioxidants.)."

In the instant case, Hattori teach that PlGF augmented the number of pluripotent hematopoietic cells by 20-fold (page 845 first column and Figure 4). Thus when used with GCSF one would expect an added benefit due to PlGF. In other words, the references teach that GCSF and PlGF individually provide beneficial results. Thus one would expect that when combined that the beneficial results would be additive. MPEP section 716.02(a) refers to greater than expected results and nonobviousness. However, in the instant case, one would expect additive beneficial effects. There is no basis to say that the results are greater than expected. Section 716.02(b) of the MPEP states that the burden is on the applicant to establish that the results are unexpected and significant. In the instant case, Hattori teach that PlGF augmented the number of

pluripotent hematopoietic cells by 20-fold (page 845 first column and Figure 4). Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4). Thus, the beneficial results when PlGF is used are not unexpected.

Although Applicants argue (reply pages 9-11) that Applicants data shows that one would not have an expectation of success, MPEP 2143.02 III states that predictability is determined at the time of the invention. As explained in the rejection one would have a reasonable expectation of success based on the express teachings of the references. Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4). Hattori teach that the studies suggest that PlGF which is endowed with a low toxicity profile provides a strategy to induce hematopoiesis after chemotherapy/radiation), or in hematological disorders (page 842 first paragraph). Since Hattori teach that PlGF augmented the number of pluripotent hematopoietic cells by 20-fold (page 845 first column and Figure 4) one would have a reasonable expectation of success. There is nothing of record to show that the data of the applicant is prior art. Thus at the time of the invention one would not have been aware of applicants data. At the time of the invention one would not have been aware of applicants data. Thus, at the time of the invention (see MPEP 2143.02 III) one would have a reasonable expectation of success based on the teachings of Hattori and Robinson. Section 2143.01 II of the MPEP discusses situations in which

the prior art conflicts. In the instant case, the record shows that the prior art (i.e. Hattori) would lead one to use PlGF. There is no prior art of record to conflict Hattori.

Although Applicants argue (reply page 11) that the evidence in the specification is valid, the evidence in the specification is not prior art. Section 2143.01 II of the MPEP discusses situations in which the prior art conflicts. In the instant case, the record shows that the prior art (i.e. Hattori) would lead one to use PlGF. There is no prior art of record to conflict Hattori.

Although Applicants argue (reply page 12) that differences are based on the intrinsic nature of the substances, both of the substances are PlGF. Hattori teach that PlGF augmented the number of pluripotent hematopoietic cells by 20-fold (page 845 first column and Figure 4). Thus when used with GCSF one would expect an added benefit due to PlGF.

Although Applicants argue (reply pages 12-15) that one cannot rely on Hattori and the correct comparison is to PlGF administered alone, Hattori is prior art. Rejections based on the prior art are based on prior art. Prior art is presumed enabled (MPEP 2121). The instant claims include 2 active agents not a single agent. Thus studies involving PlGF alone are not commensurate in scope with the claims (see MPEP 716.02(d)).

Although Applicants argue (reply pages 14-15, declaration pages 4-7) that the results are unexpected, MPEP section 716.02(c) II states that expected beneficial results are evidence of obviousness. The instant claims are drawn to compositions or methods using 2 active agents. However, the prior art already recognizes using the agents individually for certain applications. Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells. The work of Hattori (page 844 last paragraph to page 845 first paragraph and figure 4) suggest that placental growth factor mobilize

hematopoietic stem cells. Therefore, the combination of G-CSF and PlGF to mobilize hematopoietic stem cells logically flows from their having been individually taught in the prior art.

In summary, the declaration under 37 CFR 1.132 filed 11/13/09 is insufficient to overcome the rejection of the claims based upon the 103 rejections as set forth in the last Office action. The arguments provided in the declaration are discussed above. MPEP section 716.02(b) states that the burden is on the applicant to establish that the results are unexpected. MPEP section 716.02(c) II states that expected beneficial results are evidence of obviousness. The instant claims are drawn to compositions or methods using 2 active agents. However, the prior art already recognizes using the agents individually for certain applications. Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells. The work of Hattori (page 844 last paragraph to page 845 first paragraph and figure 4) suggest that placental growth factor mobilize hematopoietic stem cells. Therefore, the combination of G-CSF and PlGF to mobilize hematopoietic stem cells logically flows from their having been individually taught in the prior art. Further, since the claims require 2 active agents arguments regarding administration of PlGF alone are not commensurate in scope with the claims (MPEP 716.02(d)).

Conclusion

The 103 rejections herein is identical to the rejection set forth in the previous office action. Applicants have not amended that claims since the previous office action. In accord with section 706.07(b) of the MPEP this action is properly made final.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RONALD T. NIEBAUER whose telephone number is (571)270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anish Gupta/
Primary Examiner, Art Unit 1654

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Examiner, Art Unit 1654